Appln No.: 09/786,502
Amendment Dated: March 30, 2004
Reply to Office Action of December 31, 2003

REMARKS/ARGUMENTS

This is in response to the Office Action mailed December 31, 2003 for the above-captioned application. Reconsideration and further examination are respectfully requested.

Claims 1-6, 12-20 and 25-32 were examined. Claims 9, 14 and 15 have now been canceled. Claims 7-11 and 21-24 are withdrawn from consideration.

The Examiner indicated the sequence rules were still not complied with. The Notice to Comply with Sequence Requirement (copy attached) states that a marked up copy of the sequence listing is attached. However, no mark up was provided with applicants' copy of the office action. Thus, Applicants are unable to determine what deficiencies, if any, may exist in the filed sequence. Clarification is requested.

The Examiner rejected claim 4 as indefinite for failure to refer to a specific CD28 sequence as a reference for the base numbers. Applicants have amended claim 4 to refer to the portion that is obtained with CD28 cDNA is amplified using the primer of Seq. ID Nos. 7 and 8 as described in Example 6. Applicants submit that this amendment overcomes the rejection as presented by the Examiner. It is pointed out however, that this claim does not require the use of these specific primers, only the use of a portion of DNA that includes the portion obtained from such an amplification.

The Examiner has made several rejections under 35 USC § 103, i.e, (1)claims 1-4, 13 and 29-31 as obvious over the combination of Eshhar et al., Murphy '759 and Murphy '963; (2) claims 1-4, 6 and 17-19 as obvious over Eshhar et al., Murphy '759, Murphy '963 and Darcy; claims 1-4 as obvious over Capon '046, Murphy '759 and Murphy '963; Claims 1-4, 6 and 17-19 as obvious over Capon '046, Murphy '759, Murphy '963 and Darcy; claims 1 and 5 as obvious over Eshhar or Capon in view of Murphy '759, Murphy '963 and Alderson; Claims 1, 5 and 20 as obvious over Eshhar or Capon in view of Murphy '759, Murphy '963, Darcy and Alderson; claims 13 and 16 as obvious over Eshhar or Capon in view of Murphy '759, Murphy '963 and Gallardo. In response to Applicants' arguments that these rejections amount to nothing more than locating the bits and pieces of the present invention, with its necessary reliance on hindsight, is inappropriate, the Examiner has cited *In re McLaughlin* 443 F.2d 1392, 170 USPQ 209 (CCPA 1971) as providing legal support for the approach taken. Applicants respectfully submit that this argument is in error.

In the first place, the Examiner's reliance on *McLaughlin* does not involve looking at the facts of that case and the application of § 103 to those facts, and then comparing that to the facts of the present case. Instead, all the Examiner has done is take a line out of the case as a justification for using improper reconstruction. *McLaughlin* does not relate to biotechnology, or

to any complex art. In *McLaughlin*, the invention required a rail car with doors on diagonally oppsed ends of the opposite sides of the case, and moveable side filler panels that adjusted the width of the car at only one end. The art showed the door configuration in one reference, and the side filler panels in other references. The art further taught that both the door feature and the side panel feature could be used with palletized loads. In this circumstance, the rejection for obviousness was affirmed as prima facie obvious, although the rejection of one claim, for which secondary considerations were shown, was reversed.

The U.S. Court of Appeals for the Federal Circuit has stated that "[t]he mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification." *In re Fritch*, 972 F.2d 1260, 1266, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992) (citing *In re Gordon*, 733 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed. Cir. 1984)). Although this statement is couched in terms of modifying the prior art, it is equally applicable to combining teachings found in the prior art. Specifically, the mere fact that teachings found in the prior art could be combined as proposed by an examiner does not make the combination obvious "absent some teaching, suggestion or incentive supporting the combination." *Carella v. Starlight Archery and Pro Line Co.*, 804 F.2d 135, 140, 231 USPQ 644, 647 (Fed. Cir. 1986) (citing *ACS Hosp. Syss., Inc. v. Montefiore Hosp.*, 732 F.2d 1572, 1577, 221 USPQ 929, 933 (Fed. Cir. 1984)). This type of suggestion or motivation was present in the *McLaughlin* case because both features of the claim were known in the art to be used in the same type of railcar. The Examiner has not shown this type of connection between the references in the present case.

First of all, biotechnology is a far more complex art than railcars. The ability to make a given construct, and the functional properties of that construct cannot be said to be generally predictable. In determining obviousness, however, the properties that are disclosed for the constructs of the art and the constructs of the invention must be taken into account, and any differences between these properties is fair evidence of unobviousness. *See, In re Margolis*, 228 U.S.P.Q. 940 (Fed. Cir. 1986).

In the present application, the claims are directed to fusion protein compositions that comprise an scFv that binds to PSMA connected, optionally via a connector, to the cytoplasmic domain of a molecule that functions as a transducer of a mammalian immune response in the presence of a costimulatory factor. In claims 2 and 3, the source of the cytoplasmic domain is specified, and in claim 4 the specific portion of the CD28 cytoplasmic domain is specified. Other specific limitations are found in other dependent claims. The art takes each of these limitations, in isolation. Further, the art is selected from among myriad references that relate to other cytoplasmic domains, to other connectors, and to other scFv's to arrive at the precise combinations of the claims. There is no suggestion in any reference to choose these specific

components, however. Thus, the rejection is based entirely on the guidance of the present invention.

Looking first at claim 1, the claim recites fusion receptor composition which is a construct of a PSMA-scFv, and optional connector and a cytoplasmic domain. The cytoplasmic domain is one that functions as a transducer of a mammalian immune response in the presence of a costimulatory factor, and the fusion receptor as a whole is effective to promote a cellular immune response to PSMA. The Examiner takes the position that the primary reference, Eshhar, teaches every limitation of this claim except for the specific choice of PSMA as the antien to which the scFv is targeted. She then argues that PSMA is a known antigen and that making a fusion preceptor with the scFv for PSMA would therefore have been obvious. Implicit in this argument is the broader argument that the disclosure of Eshhar and Capon are effective to render any fusion receptor of a known scFv and a cytoplasmic domain obvious.

When one looks at the actual scope of the Examiner's argument, it bears a striking resemblance to rejections that have been deemed improper because they represent so-called obvious-to-try type of rejections. The Federal Circuit in *In re O'Farrell,* 7 USPQ2d 1673, 1681 (Fed Cir. 1988) observed that "the admonition that 'obvious to try' is not the standard under § 103 has been directed mainly at two kinds of error." This case is one of the second type, namely a case in which it may have been obvious "to explore a new technology or general approach that seemed to be a promising field of experimentation, where the art gave only general guidance as to the particular form of the claimed invention, or how to achieve it." *Id.* at 1681.

As previously argued, he Examiner has failed to establish, or even to say anything about, any reasons why the art provides an expectation of success, as opposed to some vague invitation to try a variation of the Eshhar teaching that would fall within the scope of the present claims. As noted in the present application, tests showing IL-2 stimulation, while suggestive of utility, are not dispositive since they may be followed by T cell anergy or apoptosis. This results in T cell death *in vivo* rather than the development of an appropriate immune response. (Page 3, lines 31-33; Page 14, lines 47) Insufficient costimulatory signals and perhaps other problems can render a composition effectively useless if the cells expressing the fusion does not remain alive, undergo proliferation and respond when a restimulation occurs. Eshhar, however, does not demonstrate such activity, and art such as the Alternschmidt article (cited on Page 14 of the present application) show that it may not be presumed for different antibodies than the one tested in Eshhar. The present application does demonstrate this activity for PSMA-containing species. This is a patentable and unobvious advance over the art which teaches at best techniques, and not the claimed invention.

This same over-generalization infects the remainder of the rejections. For example, claims 4, 19, 27 and 31 refer to a specific portion of the CD28 cDNA, yet the Examiner has not shown anywhere in the art where the use of this portion is taught or suggested.

With respect to claims 5, 20, 28, and 32, the cytoplasmic domain is identified as being a 41-BB cytoplasmic domain. The Examiner's secondary reference, Alderson, does nothing more than state that this receptor exists. There is nothing in the abstract (all that was cited by the Examiner) of use of this molecule in a fusion construct with anything let along a PSMA-scFv. Thus, the Examiner has taken the idea of a fusion construct from the primary reference, selected a replacement scFv from among the many in the art based solely on the guidance of the application, and then selected a receptor from among the many known in the art, again based solely on the present application to arrive at a supposedly obvious combination. There is no reasoning offered for this substitution besides a technically naive concept that all T cell receptors are equivalent and interchangeable.

Furthermore, as previously noted, but not responded to, based solely on the abstract of Alderson, the Examiner states that the reference teaches that 4-1BB is a T-cell receptor. What the abstract actually states is that 4-1BB is shown to be a member of the tumor necrosis factor receptor family. Since the motivation to use 4-1BB is based on the identification of it as a T cell receptor, it is necessary for the Examiner to provide an explanation of why one skilled in the art would equate a TNF receptor with the receptors of the Eshhar or Capon references. This has not been done. Furthermore, even with such an explanation, the rejection would still suffer from the same flaw as discussed above. Furthermore, the Examiner states that the reference discloses the sequence of 4-1BB, although there is no statement in the abstract, nor even a statement that the full paper discloses the sequence. The basis for this statement of the Examiner is therefore not understood.

With respect to the specific recitation in claims 6, and 17-19 of the incorporation of a CD8 hinge section as the connector, the Examiner cites a reference which uses a different scFv from the claimed invention, a γ receptor domain and a CD8 hinge. The Examiner's entire argument is that because the CD8 hinge is used in this molecule, putting it in any other fusion, including that now being claimed would have been obvious. The Examiner has not, however, pointed to any suggestion in the references that the CD8 hinge is of such general applicability, nor explained why such applicability would be expected based on what is taught. Thus, the Examiner has merely found the pieces of the claimed invention in the art and has not made the connections required to support an obviousness rejection. See, *Ex Parte Hiyamizu*, 10 USPQ 2d 1393, 1394 (POBAI 1988)("Citing references which merely indicate the isolated elements ... are known is not a sufficient basis for concluding that the combination of elements would have been obvious.").

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The Examiner has made similar rejections of the claims substituting US Patent No. 5,369,046 of Capon for the Eshhar disclosure. Applicants have previously pointed out to the Examiner that the characterization of Capon is in error to the extent it concludes that the antibodies described in Capon are formed from antibodies that have just the variable regions. As previously observed, the antibodies of Capon include substantial amounts of the constant regions (CH1, CH2 etc). The usage in the Capon patent of the term "single chain antibody" is inconsistent with accepted usage in which the term scFv is defined as "scFv: A single chain molecule composed of the variable regions of an antibody heavy and light chain joined together by a flexible linker." http://www.roitt.com/glossary.htm#s. Thus, the Capon reference is even less similar to the claimed invention than Eshhar. The Examiner has not responded to this argument, nor said how this additional difference between Capon and the claimed invention can be considered irrelevant.

For these reasons, this application is now considered to be in condition for allowance subject to the submission of a corrected sequence listing when the details of the alleged defect are received from the patent office. Such action is earnestly solicited.

Respectfully Submitted,

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